NONLIPID RETICULO-ENDOTHELIOSIS: LETTERER-SIWE'S DISEASE

A Report of Three Cases *

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A clinicopathologic syndrome involving principally the reticulo-endothelial system in infants and young children and having a fatal outcome has come to be known as Letterer-Siwe's disease since the publication of an article by Abt and Denenholz [1] in 1936. In 1942 Green and Farber [2] postulated a possible relationship between Letterer-Siwe's disease, Schüller-Christian's disease, and eosinophilic granuloma of bone. A more general awareness of the disease and its possible relationship to Schüller-Christian's disease and eosinophilic granuloma should stimulate the reporting of additional cases of diseases involving the reticulo-endothelial system. This will aid in the clarification of these disease entities, if indeed they are such, or will serve to classify them properly as variants of a single disease process. With this in mind, three cases of Letterer-Siwe's disease autopsied at this Institute since November, 1940, are reported in detail. These cases fulfill the requirements for Letterer-Siwe's disease as formulated by Abt and Denenholz, namely: splenomegaly, hepatomegaly, generalized lymphadenopathy, localized tumors either over or in bone, secondary anemia, generalized hyperplasia of the cells composing the reticulo-endothelial system, a nonfamilial disease of infants terminating fatally.

Report of Cases

Case 1

A 4½-months-old white male infant was admitted to Babies and Childrens Hospital, Cleveland, on November 9, 1940, because of "white patches on the gums and tonsils and a lump on the right side of the head." Except for a cutaneous eruption stated to be present from birth, which had never completely disappeared, the infant was well until the age of 2½ months, when he developed anorexia, "colic," and an otitis media which required bilateral myringotomy. Examination on both occasions revealed cutaneous petechiae and enlarged tonsils. At 4 months, multiple buccal ulcers and a small lump in the right temporal region were noted. The parents and one sibling were alive and well.

Examination on admission revealed a well nourished infant. Over the trunk were many cutaneous lesions, petechiae, and yellow to dark-red papules, many less than 1 mm. in diameter (Fig. 1). Covering the scalp were small, yellow, crusted lesions. In the right temporal region was a subcutaneous, soft mass measuring 1.5 cm. in maximum diameter. Two shallow ulcers were found on the alveolar process of the maxilla. The tonsils were covered by a pale-gray exudate. The liver was palpable 2.5 cm. below the costal margin in the right midclavicular line. Several

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defects in the skull were palpable through the scalp: one, measuring 1 by 1.5 cm., was beneath the mass in the right temporal region; a slightly larger one was present in the right occipital region; and a third was present in the right parietal region.

Laboratory Examinations. Blood: red blood cell count, 5,600,000; hemoglobin, 94 per cent (Sahli); white blood cell count, 12,000, with 78 polymorphonuclear leukocytes, 20 small lymphocytes, and 2 mononuclear cells per 100 white blood cells; serum cholesterol, 132 mg.; cholesterol esters, 75 mg.; total fat, 656 mg.; and lecithin, 195 mg. per 100 cc. Urine showed a trace of albumin, with 2 or 3 white blood cells per low-power field. Roentgenograms of the skull showed three irregularly rounded, radiolucent areas as follows: One, 1.5 cm. in diameter, in the anterior and inferior portion of the right parietal bone; another, 1 cm. in diameter, in the same bone near the lamboidal suture; and a third, 3 cm. in diameter, in the occipital bone (Fig. 2). The long bones, ribs, and pelvis showed no abnormalities roentgenologically except an area of lessened density at the proximal end of the right humerus on the medial aspect, 0.1 by 0.5 cm. in size. Roentgenograms of the chest showed a peculiar fine "honey combing" of the entire lung fields and a mottled appearance of each apex to the level of the 4th rib.

During the 8 days the infant was in the hospital the temperature remained below 38°C. except on the first day when it rose to 38.9°C. Dyspnea which was noted on the day of admission became progressively worse and was not relieved by administration of intranasal oxygen. On November 16, subcutaneous emphysema of the neck and upper thorax was observed and the infant died later that day. The clinical diagnosis was Schüller-Christian's disease and bilateral chronic suppurative otitis media.

Autopsy (no. 7184) was performed by Dr. F. M. Barry, 3 hours after death.

Gross Description. The body was that of a white male infant weighing 6,250 gm. Inspection of the skin and mucous membranes and palpation of the skull and subcutaneous tissues of the neck confirmed the presence of cutaneous and buccal lesions, osseous defects, and emphysema as described previously. The thymus was of normal size, its cut surfaces were lobulated, pale-brown mottled with yellow and flecked with firm, circumscribed, white foci measuring 2 to 3 mm. in diameter. The thyroid weighed 5 gm. The heart weighed 41 gm. (expected weight, 29 gm.) and, except for hypertrophy, was grossly normal. The lungs were pale-pink mottled with gray. On their surfaces were many bullae measuring from 0.1 to 2 cm. in diameter. These had thin, transparent walls and contained air. One along the upper border of the left lung was ruptured and probably was the source of the mediastinal and subcutaneous emphysema. Air spaces measuring 0.1 to 2 cm. in diameter were surrounded by firm septa which were pale pinkish tan mottled with yellow, and measured 0.2 to 0.5 cm. in width, imparting a "honey comb" appearance to the pulmonary parenchyma. The larynx, trachea, and bronchi were normal. The liver weighed 275 gm. (expected weight, 188 gm.), and was grossly normal. The gastro-intestinal tract showed no abnormalities except that the lymphoid tissue of the small and large

intestines was more prominent than usual. The solitary follicles measured up to 0.1 cm. in diameter. The pancreas, adrenals, kidneys, urinary bladder, prostate, and testes were all normally located and showed no lesions grossly. The spleen weighed 30 gm. (expected weight, 16 gm.). Gray follicles, 1 mm. in diameter, surrounded by dark-red pulp were seen on the cut surface. All the lymph nodes throughout the body were enlarged, measuring from 0.5 to 1.5 cm. in diameter. They were pale yellow and firmer than is normal. Their cut surfaces were homogenous and lacked their usual pattern. The brain, which weighed 750 gm. (expected weight, 420 gm.), was grossly normal. The skull bones varied greatly in thickness, in some places being less than 2 mm. There were three osseous defects with smoothly rounded margins, occupying positions as shown by the roentgenograms (Fig. 2). These defects were composed of firm, reddish brown tissue overlying but not adherent to the dura. There was no apparent abnormality of the bones of the orbit, sella turcica, or base of the skull. There was a small perforation in each tympanic membrane. The bone marrow of the sternum, ribs, and vertebrae was reddish brown and of normal consistency.

The microscopic observations on this case and the succeeding two cases will be described together following the gross observations on the third case. The similarity between the lesions of the various organs can be more effectively depicted in this manner.

Case 2

This 8-months-old male infant was seen by a pediatrician 1 week before admission to Babies and Childrens Hospital on June 20, 1945, because of fever and "sores on the gums." The liver and spleen were palpable and a blood count showed moderate leukocytosis. A tentative diagnosis of leukemia was made. The parents stated that at birth the infant had had petechiae over the body and hands which disappeared with the administration of vitamin K. Five weeks before the present illness, a light brown, crusted and scaling eruption appeared over the body and petechiae were noted on the hands, face, and trunk. The infant had been listless for several weeks, he cried when handled, his breathing was more rapid, and his skin paler than usual. The parents and 3 siblings were alive and well.

On admission the child appeared acutely and chronically ill; temperature, 39.9°C.; pulse, 148; and respirations, 60. The skin and mucous membranes were pallid and many petechiae were present over the trunk, being most numerous on the upper back and back of the head (Fig. 3), but not present on the arms, legs, or feet. Several bullous lesions, 2 cm. in diameter, and containing clear, pale-yellow fluid, were present on the buttocks and inner aspects of the thighs. Elsewhere the skin was dry and scaling. The anterior maxillary, cervical, and axillary lymph nodes were palpable, firm, and discrete. The liver was palpable 4 cm. below the right costal margin and the spleen, 4 cm. below the left costal margin.

Admission Laboratory Examinations. Blood: Red blood cell count, 2,400,000; hemoglobin, 38 per cent (Sahli); white blood cell count, 20,500; platelet count, 450,000; 77 polymorphonuclear leukocytes, 20 lymphocytes, 2 mononuclear cells,

and 1 eosinophil per 100 white blood cells; bleeding time, 4 minutes 15 seconds; clotting time, 1 minute 45 seconds; prothrombin time, 80 seconds (normal, 30 seconds); serum protein, 6.1 gm.; cholesterol, 100 mg.; cholesterol esters, 36 mg.; total fat, 716 mg.; lecithin, 209 mg.; calcium, 7.3 mg.; phosphorus, 3.4 mg.; nonprotein nitrogen, 35 mg. per 100 cc. of blood; culture, no growth after 6 days; Wassermann and heterophile antibody agglutination tests, negative. Urine: normal. Roentgenograms of the skull and extremities showed no osseous defects. Roentgenograms of the chest showed a widened supracardiac shadow, with increased hilar bronchovascular markings. A splenic puncture showed atypical mononuclear cells suggestive of xanthomatosis (lipidosis).

Throughout his hospital course the patient was acutely ill. Penicillin and sulfadiazine were given without effect on the patient's fever, which showed daily elevations from 38° to 40°C. Supportive measures, consisting of transfusions, hykinone, and ascorbic acid, were used without permanent improvement. The red blood cell count and hemoglobin increased slightly as a result of repeated transfusions, but there was a progressive decrease in the number of white blood cells. The patient lost weight rapidly, with marked wasting of the extremities and edema of the neck and head. He died on the 22nd hospital day. The clinical diagnosis was lipidosis, possible Niemann-Pick's or Gaucher's disease.

Autopsy (no. 8862) was performed by Dr. G. S. Wilson, 6½ hours after death.

Gross Description. The body was that of a poorly nourished, white male child weighing 11 kg. The cutaneous lesions of the body and scalp were as described in the clinical abstract. There was hemorrhage into the right leaf of the diaphragm and 60 cc. of blood-tinged fluid in the peritoneum. The thymus, which weighed 13 gm. (expected weight, 18 gm.), was lobulated, reddish brown, and firm. The cut surfaces were reddish brown as compared to the normal pale pinkish or grayish tan. The heart weighed 53 gm. (expected weight, 37 gm.) and, except for size, was normal in all respects. The lungs were uniformly grayish pink and well expanded, but crepitation was decreased throughout. The liver weighed 550 gm. (expected weight, 254 gm.). Sections revealed nonbulging, reddish brown surfaces upon which the lobular pattern was faintly discernible. The esophagus, stomach, small and large intestines, pancreas, adrenals, kidneys, urinary bladder, prostate, and testes were all normally located and not remarkable grossly. The spleen was markedly enlarged, weighing 200 gm. (expected weight, 20 gm.). It was firmer than average, and sections made against increased resistance revealed surfaces which were brownish red flecked with multiple scattered, pale brownish gray foci measuring up to 3 and 4 mm. in diameter. An accessory spleen, measuring 1 cm. in diameter, resembled the spleen in color and consistency. The cervical, axillary, mediastinal, suprapancreatic, mesenteric, and para-aortic lymph nodes were firm, discrete, and enlarged to approximately three times their normal size. Cut surfaces were flat, firm, and brownish red mottled with gray. The brain

weighed 780 gm. (expected weight, 714 gm.) and was grossly normal. Examination of the skeletal system showed no osseous lesions. The marrow from the sternum, ribs, and lumbar vertebrae was of average consistency and pale brownish red. The skull bones were normal. The middle ear and mastoid air cells showed no evidence of inflammation.

Case 3

A white male infant was admitted to Babies and Childrens Hospital on December 20, 1945, at the age of 3 weeks because of diarrhea, vomiting, and fever. The infant was born at term of a 23-year-old primipara who was well during her pregnancy. A generalized cutaneous eruption had been present at birth. This was described by a pediatrician as a "polymorphous rash consisting of petechiae, red macules and pale tan scaly crusts." During the first week the eruption cleared spontaneously except for small crusted lesions of the scalp. The infant vomited his feedings frequently and had gained weight slowly. Three days before admission he became irritable and a hoarse cry developed; the following day he had 10 to 12 watery, pale yellow stools. One day before admission a generalized cutaneous eruption again appeared, beginning as petechiae over the lower extremities and progressively spreading over the trunk and becoming macular and papular.

On admission the infant appeared neither acutely nor chronically ill but his cry was hoarse. There was a generalized papular and macular eruption over the entire body except the face, palms of the hands, and soles of the feet. Petechiae were scattered among the other lesions. Yellow crusted lesions were present in the scalp, and red macules on the hard palate. Lymph nodes, except the inguinal, were not palpable; these were small, firm, and discrete. The abdomen was distended and tympanitic but the liver and spleen could be palpated, the liver 5 cm. below the right costal margin, the spleen 4 cm. below the left costal margin.

Laboratory Examinations. Blood: Red blood cell count, 3,900,000; hemoglobin, 82 per cent (Sahli); white blood cell count, 6,600, with 50 neutrophilic polymorphonuclear leukocytes, 46 lymphocytes, 2 mononuclear cells, and 2 eosinophils per 100 cells; platelets were present in normal numbers; serum cholesterol, 150 mg.; total fat, 484 mg.; lecithin, 274 mg. per 100 cc. Urine: normal. Roentgenograms of the skull and long bones showed no osseous defects; the lungs were normal. A blood culture taken on the 18th hospital day showed no growth after 6 days.

The patient was given sulfadiazine, 0.5 gm. on admission and 0.125 gm. every 4 hours thereafter for 15 days. He was given Ringer's solution by mouth and parenteral fluids until the diarrhea was under control on the 2nd hospital day. The temperature rose to 39.5°C. on the 2nd and 3rd hospital days, then fell to normal. Diarrhea reappeared on the 8th hospital day and could not be controlled by the usual methods. The weight, which had increased to 3,250 gm., fell to 2,800 gm. and remained there even after marked edema appeared on the 18th hospital day. The lesions of the palate progressed to form confluent, shallow ulcers with gray, firm margins and bleeding bases. On the 19th hospital day the red blood cell count was 1,300,000; the hemoglobin, 38 per cent; white blood cell count, 9,000. Many of the lymphocytes in the blood smear had vacuolated cytoplasm and several blast forms contained vacuoles. The patient died on the 20th hospital day. The clinical diagnosis was reticulo-endotheliosis, probably Letterer-Siwe's disease.

Autopsy (no. 9042) was performed by Dr. A. H. Salans, 3½ hours after death.

Gross Description. The body was that of an emaciated white male infant weighing 2.8 kg. Inspection revealed cutaneous and buccal lesions, and edema as noted in the clinical history. The thymus weighed 4.5 gm. (expected weight, 10 gm.). The external and cut surfaces were firm, lobulated, and yellow brown mottled with purplish red. The thyroid weighed 1 gm. and was normal grossly. The heart weighed 17.5 gm. (expected weight, 12 gm.). The right ventricle was slightly dilated; otherwise the heart was normal. The right and left lungs weighed 32 and 26 gm. respectively and, except for slightly reduced crepitation, were normal grossly. The liver weighed 133 gm. (expected weight, 80 gm.). The cut surfaces were nonbulging, deep purple, and without definite markings. The Peyer's patches of the ileum and the solitary lymphoid follicles of the terminal ileum and colon were more prominent than expected. In the latter situation they measured up to 0.2 cm. in diameter and had umbilicated centers. The remainder of the gastrointestinal system was normal grossly. The adrenals and genito-urinary system showed no gross abnormalities. The spleen weighed 22.5 gm. (expected weight, 8 gm.). Cut surfaces showed faintly visible, pale gray follicles surrounded by deep reddish purple tissue. The mesenteric lymph nodes were enlarged, measuring up to 1.5 cm. in diameter. Cut surfaces were pale pink, mottled with gray, circular foci averaging 1 mm. in diameter. The peribronchial and mediastinal lymph nodes were not remarkable. Bone marrow from the lumbar vertebrae was pinkish brown mottled with gray. The autopsy permit did not include examination of the long bones, skull, and brain.

MICROSCOPIC OBSERVATIONS

The characteristic cutaneous lesions showed collections of large atypical mononuclear cells and small hemorrhages in the corium. There was parakeratosis with scale formation (Fig. 4) and atrophy of overlying epithelium. A few polymorphonuclear leukocytes were present in the epidermis and corium. In case 2, scaling was not a prominent feature (Fig. 5). The cutaneous lesions in case 3 showed sparsely scattered eosinophils in the corium and atypical mononuclear cells in the subcutaneous fat, in addition to the above changes.

Sections of the thymus showed no recognizable thymic tissue in cases 1 and 2. In case 3 a rare Hassall's corpuscle could be identified. Traversing the gland and dividing it into lobules were narrow bands of fibrous tissue and intermingled fibroblasts. The substance of the gland was composed of loosely arranged cells of several different types. Relatively large cells, approximately 12 to 20 μ, were predominant in all

cases. These were of irregular outline, with acidophilic cytoplasm and centrally or eccentrically placed vesicular nuclei, which varied in shape, some being oval, other lobulated and grooved, and still others irregularly "crumpled." Chromatin was irregularly distributed in the nuclei and no nucleoli were noted except in case 3. Many of the atypical cells in this case contained large violaceous nucleoli. Mitotic figures were infrequent in each case. The cytoplasm of some of the atypical cells in cases 1 and 2 was vacuolated. There were scattered foci of large multinucleated giant cells having 4 to 12 nuclei and irregular cell borders. Many showed phagocytosis of brown pigment, erythrocytes, and polymorphonuclear leukocytes (Fig. 6). Multinucleated forms were smaller and less numerous in cases 2 and 3. Scattered eosinophils and foci of small lymphocytes were present in each thymus. Portions of each gland were unusually vascular and capillary proliferation was conspicuous. Rare foci of necrosis, approximately one-sixth the diameter of a low-power field, were seen in case 2. Special stains revealed sudanotropic droplets in the cytoplasm of some of the large mononuclear and giant cells, but examination of the tissues under crossed Nicol prisms showed no doubly refractile crystals. Sections treated with hydrochloric acid and ferrocyanide showed a moderate amount of iron pigment within phagocytic cells.

In only the first case did the thyroid show involvement by characteristic lesions composed of large atypical mononuclear cells. Foci of these cells formed nodules in the interlobular connective tissue and in some instances projected into acini.

Sections of the heart and aorta were normal in all cases except the first, which showed small hemorrhages in the myocardium and endocardium.

The amount of pulmonary tissue involved by reticulo-endothelial cells and the degree of bronchopneumonia varied in the three cases. In case 1 the changes were predominantly interstitial. Alveolar walls were thickened by virtue of an increase in the cellular constituents. These cells were principally of the type previously described. Atypical mononuclear cells were free also within alveoli; an occasional cell contained sudanotropic droplets. A few lymphocytes and neutrophilic and eosinophilic polymorphonuclear leukocytes were admixed with the atypical mononuclear cells. Interlobular septa, peribronchial and perivascular tissue, and included portions of the pleura contained similar cells in variable numbers. Some were observed within lumina of blood vessels. Emphysema was conspicuous in some sections and there was a small focus of bronchopneumonia in the left lower lobe. In case 2 the

interstitial changes, while similar, were less profound than in the previous case. There was a small focus of bronchopneumonia in the right middle lobe. The last case showed the least interstitial involvement by large atypical mononuclear cells. A section from the right upper lobe showed a nodule composed chiefly of these cells (Fig. 7). Sections of the larynx and trachea in this case showed many fibroblasts in the subepithelial connective tissue and scattered foci of polymorphonuclear cells.

Except for diffuse cloudy swelling of hepatic cells and fatty metamorphosis, changes in the liver in case 1 were slight. A few Kupffer cells were enlarged and there was a slight increase of connective tissue in the portal regions. A small nodule of atypical mononuclear cells was present within the wall of a bile duct. In cases 2 and 3, many Kupffer cells were enlarged and showed phagocytosis of polymorphonuclear leukocytes and erythrocytes. The connective tissue of the portal regions was greatly increased and contained many large atypical mononuclear cells, some of these forming nodules of 12 to 16 cells. Foci of hematopoiesis were numerous in case 3. Eosinophils not confined to these foci numbered 12 to 15 per high-power field. Several foci of atypical mononuclear cells were present in the interlobular connective tissue of the pancreas in the first and second case.

A section taken through the gingival ulcer in the first case showed a layer of large atypical mononuclear cells of the type seen elsewhere, covered by neutrophilic polymorphonuclear leukocytes mixed with fibrin. The atypical cells were grouped in nodules. Some of the cells contained mitotic figures and some bizarre nuclei (Fig. 8). Sections from the remaining portions of the gastro-intestinal tract in each case differed only in degree of involvement of the interglandular and lymphoid tissue by atypical cells. This was less in the stomach and jejunum. The lymphoid follicles and Peyer's patches were partially replaced by large mononuclear cells (Fig. 9). Mitotic figures were observed in every 2 or 3 high-power fields. Eosinophils numbered 6 to 10 per high-power field. These changes were most profound in case 3 in which the mucosa of the jejunum, ileum, and colon was increased two to three times its normal thickness because of the large number of atypical cells in the interglandular stroma. The mucosa over the Peyer's patches and lymphoid follicles was ulcerated.

Diffusely scattered throughout the loose peripelvic connective tissue of the kidneys were large atypical mononuclear cells. In addition there was a small circumscribed nodule of similar cells in the cortex of the right kidney in case 2. In this case sections from the testes showed numerous atypical cells in the connective tissue underlying the tunica

vaginalis and in the interlobular septa; in the latter situation they occasionally formed nodules of 15 to 20 cells. The testes in the other two cases showed no abnormal changes.

In case 3 the medullary cells of the adrenal were replaced mostly by atypical mononuclear cells mixed with a few eosinophils. Similar cells were present in the pericapsular fat and some of these exhibited phagocytosis of erythrocytes.

In cases 2 and 3 the normal pattern of the spleen was considerably altered by the presence of large numbers of atypical mononuclear cells. In case 1 the general pattern was retained even though nodules composed of 12 to 30 large mononuclear cells formed the centers of most of the follicles (Fig. 10). In all cases there was endothelial hyperplasia of central arterioles and sinuses. Phagocytosis of erythrocytes and of brown pigment was conspicuous, particularly in cases 1 and 2.

Sections from many lymph nodes in all cases were similar but varied considerably in degree of involvement. In case 1 the general microscopic appearance was similar to that in the thymus except that giant multinucleated cells were scarce. In case 2 the normal pattern was more or less well preserved, with an increase of large mononuclear cells in the central portions and peripheral sinuses. Phagocytosis of polymorphonuclear leukocytes and erythrocytes by the reticulo-endothelial cells in the para-aortic lymph nodes was conspicuous. Many of these cells had vacuolated cytoplasm (Fig. 11). In case 3, eosinophils were relatively numerous. One lymph node from the mesenteric group contained several minute abscesses surrounded by mononuclear cells. In the tonsils of case 1 the lymphoid tissue was replaced by nodules of atypical mononuclear cells, which penetrated deeply into the underlying tissue and in some foci extended into striated muscle. No sudanotropic droplets were demonstrated in the reticulo-endothelial cells of the spleen, lymph nodes, or tonsils in case 1, but they were present in the vacuolated cells of the para-aortic lymph nodes in case 2 and in scattered mononuclear cells in lymph nodes, pulmonary alveoli, and cutaneous lesions in case 3.

Special stains showed inconstant amounts of reticulin where the reticulo-endothelial cells were most numerous. In some instances fibrils of reticulin were in intimate association with these cells. In other sites a small amount of reticulin surrounded foci or nodules of these cells in the spleen and lymph nodes but the fibrils did not extend among the cells. None was observed in association with the large mononuclear cells of the cutis in case 3, yet there was a heavy reticulin network in the pulmonary nodule composed of these cells in the same case.

A section through one of the cranial defects in case 1 revealed dense

fibrous connective tissue replacing the bone. Foci of cells, similar to those described as reticulo-endothelial elsewhere, were present. Adjacent to this defect the usual two tables of compact bone were present but the bone marrow contained many foci of large, irregularly shaped reticulo-endothelial cells. Bone marrow from the sternum in case 2 and from a lumbar vertebra in case 3 showed a few large atypical mononuclear cells among the normal cellular components.

The anatomic diagnoses in case 1 were: Reticulo-endotheliosis (nonlipid) of skin, gums, thymus, thyroid, lungs, liver, pancreas, lymphoid tissue of gastro-intestinal tract, pelvis of kidneys, spleen, lymph nodes, tonsils, bones of skull, and bone marrow; bronchopneumonia of lower lobe of left lung; emphysema of lungs; emphysema of tissues of anterior mediastinum and subcutaneous tissues of face, neck, and upper anterior thorax; fatty metamorphosis of liver; perforations of tympanic membranes (recent bilateral myringotomy).

The anatomic diagnoses in case 2 were: Nonlipid reticulo-endotheliosis (Letterer-Siwe's disease) involving skin, thymus, lungs, liver, pancreas, lymphoid tissue of intestines, kidneys and peripelvic fat, testes, pars nervosa of pituitary body, spleen, lymph nodes, and bone marrow; bronchopneumonia of middle lobe of right lung; recent hemorrhage into right leaf of diaphragm; hemoperitoneum.

The anatomic diagnoses in case 3 were: Nonlipid reticulo-endotheliosis (Letterer-Siwe's disease) involving skin, thymus, larynx, liver, lymphoid tissue of intestines, spleen, lymph nodes, bone marrow, adrenals, and periadrenal and subcutaneous fat; bronchopneumonia; hematopoiesis of liver; edema of peri-orbital tissues, hands, and feet.

Comments

The remarkable similarity of the clinical courses and of the anatomic and microscopic observations in the foregoing cases leaves no doubt that they belong in the category of reticulo-endotheliosis known as Letterer-Siwe's disease. All showed a cutaneous eruption, pronounced hepatomegaly and splenomegaly, and variable degrees of lymphadenopathy at the time of hospitalization. Other presenting symptoms (mass over the right temporal bone in case 1, buccal ulcers in cases 1 and 2, diarrhea and hoarseness in case 3) may all be explained by localized proliferation of reticulo-endothelial cells. The course of the disease in all three instances was rapid and accompanied by a progressive anemia in cases 2 and 3. Only on admission was a blood count done on case 1, and this showed no anemia, but anemia probably did develop later. The fatal termination of these cases is in accord with other reports of this

TABLE I

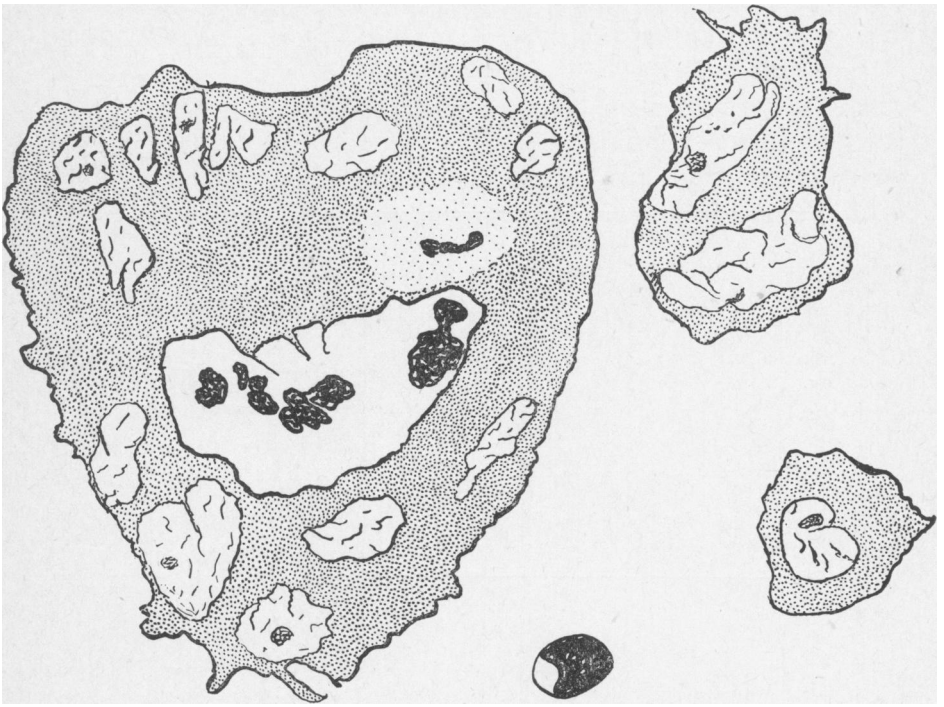
Summary of Pertinent Observations on the Clinical Course, Physical and Laboratory Examination

	Case 1	Case 2	Case 3
Sex and race	Male, Gentile	Male, Gentile	Male, Gentile
Age	4½ months	8 months	3 weeks
Presenting symptom	"Lump," right side of head	Pallor, "buccal ulcers"	Diarrhea
Fever	38.9°C.	39.9°C.	39.5°C.
Liver	Palpable	Palpable	Palpable
Spleen	Not palpable	Palpable	Palpable
Lymph nodes	Not palpable	Axillary, cervical, maxillary: palpable	Inguinal: palpable
Cutaneous eruption	From birth	Petechiae at birth	Polymorphous rash at birth
Osseous lesions	Multiple defects in skull, defect in proximal end of right humerus	None by x-ray	None by x-ray
Red blood cell count	5,600,000 (hemoglobin, 94%)	2,400,000 (hemoglobin, 38%)	3,900,000 (hemoglobin, 82%)
White blood cell count	12,000	20,500	6,600
Platelets	Not recorded	450,000	Normal numbers
Serum cholesterol	132 mg./100 cc.	100–135 mg./100 cc.	150 mg./100 cc.
Serum lecithin	195 mg./100 cc.	206 mg./100 cc.	274 mg./100 cc.
Total fats	656 mg./100 cc.	716 mg./100 cc.	484 mg./100 cc.
Duration	Approximately 2 months	3–4 weeks	23 days

condition. Table I summarizes the pertinent observations relative to the clinical courses, physical and laboratory examinations.

In all cases the anatomic and morphologic features were similar. There was universal involvement of the cells of the reticulo-endothelial system. The marked proliferation or hyperplasia of these cells resulted in an increase in the size of those organs having a conspicuous reticulo-endothelial component. This hyperplasia was both diffuse and focal. In the latter instance it resulted in the formation of nodules. While the individual cells varied slightly in size from case to case and sometimes from organ to organ in the same case, they were strikingly uniform in other respects. Text-Figure 1 is a camera lucida drawing of typical cells from the thymus in case 1, which shows some of the salient characters of these cells. Text-Figure 2 is

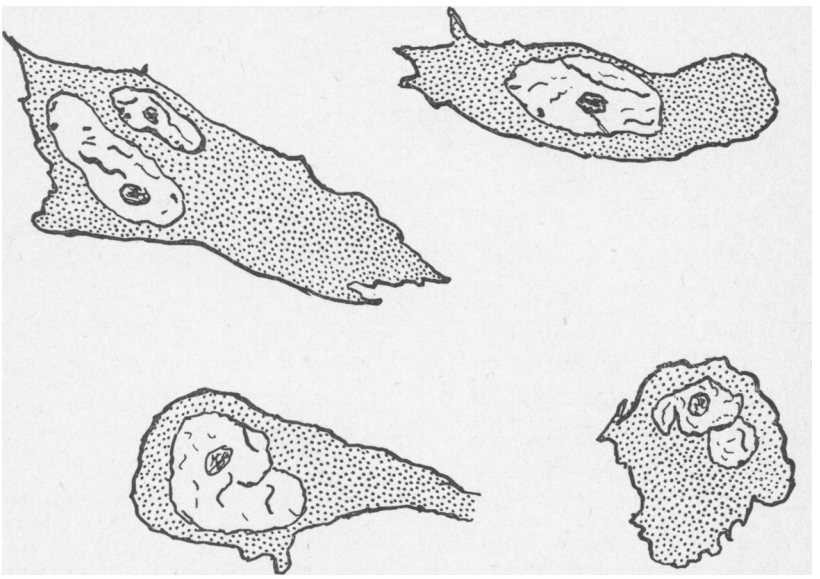
a camera lucida drawing of typical cells seen in the spleen in the same case. Another noteworthy feature was the endothelial and fibroblastic proliferation observed in some of the granulomatous lesions of certain organs, principally, the thymus, lungs, and spleen.



Text-Figure 1. Camera lucida drawing of typical cells seen in the thymus in case 1. The giant cell contains phagocytized leukocytes. A clear halo surrounds the nuclear remnants of several of these cells. The small cell with a dark nucleus in lower center field is a lymphocyte, for comparison of the relative size of the cells.

Even though cutaneous lesions differed slightly on gross examination in the three cases, the microscopic appearance was strikingly similar (Figs. 4 and 5). Few organs escaped involvement by reticulo-endothelial hyperplasia. The thymus showed the most striking changes, being unrecognizable on microscopic examination alone in cases 1 and 2. The significance of these constant and profound changes is not known. The lungs, liver, spleen, and lymphoid tissue were constantly but variably involved. The lungs showed the most profound changes in case 1. The degree of hepatic involvement varied considerably, and microscopically did not seem sufficient to cause hepatomegaly. Splenic involvement resulted in splenomegaly. In case 2, the spleen was ten times the expected size. The lymph nodes and the lymphoid tissue of the gastro-intestinal tract showed similar changes. This involvement did not result

in marked lymphadenopathy, nor in unusual increase in size of the solitary follicles and Peyer's patches of the intestines except in case 3. The endocrine glands were not universally involved by reticulo-endothelial proliferation. The only glands so involved were the thyroid in case 1, the testes and pituitary body in case 2, and the adrenals in case 3. The bone marrow showed slight to moderate involvement in all instances, with groups of reticulo-endothelial cells replacing the normal cells of the bone marrow. This change, if extensive, may be a factor in the production of anemia of the progressive nonregenerative type which occurs in Letterer-Siwe's disease. Only in case 1 did the changes produce osseous defects, visible on roentgenographic examination.



Text-Figure 2. Camera lucida drawing of typical cells from the spleen in case 1. Of note are the irregular cell outline and large vesicular nuclei.

While phagocytic activity of the reticulo-endothelial cells was observed in all cases, it was particularly profound in cases 1 and 3. This property of the reticulo-endothelial cells might explain the presence of lipid in some of the cells. In case 3 the phagocytic activity was concerned chiefly with the ingestion of erythrocytes. If pronounced, this activity may be an additional factor in the production of anemia. Another noteworthy microscopic feature was the presence of mitotic figures in the foci of hyperplasia. This observation has not been uniformly reported.

Review of Literature

In 1936 Abt and Denenholz [1] reported a case of nonlipid reticulo-endotheliosis in an infant, which fulfilled the criteria established by

Siwe [3] in 1933. The first case was reported by Letterer,[4] in 1924, as proliferative aleukemic reticulosis. The second and third cases were those of Akiba [5] and Guizetti [6] reported in 1926 and 1931. Siwe reported the fourth case and reviewed the 3 previous cases. Abt and Denenholz included in their series the cases of Podvinec and Terplan [7] (1931), Gittins' [8] case 4 (1933), and the cases of Foot and Olcott [9] (1934), and of Roussy and Oberling [10] (1934). These cases are ably summarized by them [1] (Table 2, page 506). A case by van Creveld and Ter Poorten,[11] reported in 1935, was not accepted as a noninfectious reticulo-endotheliosis because the infant had had an otitis media from the age of 4 weeks. This case had defects of the membranous bones of the skull and cystic lesions of the humeri and ribs. Abt and Denenholz also excluded a case by Schultz, Wermbter, and Puhl.[12] Siwe believed this to be an atypical case of Schüller-Christian's disease and it was similarly classified by Abt and Denenholz.

In September, 1940, Wallgren [13] reported 2 cases and reviewed 15 cases. He included those reported by Abt and Denenholz [1] and added several which had been reported as infectious nonlipid reticulo-endotheliosis. The cases of Schultz, Wermbter, and Puhl [12] (1924), Krahn [14] (1926), Sherman [15] (1929), Gittins' case 2 [8] (1933), Uher [16] (1933), Klostermeyer [17] (1934), and of van Creveld and Ter Poorten [11] (1935) were regarded by Wallgren as infectious nonlipid reticulo-endotheliosis. The cases of Podvinec and Terplan,[7] and of Foot and Olcott,[9] cited by Abt and Denenholz as noninfectious nonlipid reticulo-endotheliosis, were thought by Wallgren to be infectious reticulo-endotheliosis. It is interesting to note that Akiba [5] regarded his own case as being related to an infection, yet both Wallgren, and Abt and Denenholz classified it as a noninfectious reticulo-endotheliosis. Similarly, Letterer,[4] Guizetti,[6] Podvinec and Terplan,[7] and Foot and Olcott [9] thought that possibly infection was an etiologic factor in their cases. These cases, 17 in all, were summarized by Wallgren and will not be reviewed further here except to state that Sherman's case [15] probably does not belong in this category. This case, which showed marked hyperplasia of the reticulo-endothelial system without granulomas, occurred in an 11-day-old infant that had erysipelas, streptococcal septicemia, and jaundice. Klostermeyer's case [17] is regarded as a lymphoid leukemia by several investigators.

Paige [18] presented 2 previously unreported cases of Letterer-Siwe's disease in 1935. Between 1936 and 1940 no additional cases appeared in the literature. A critical review reveals a number of cases, appearing under various titles, which probably belong to this clinicopathologic

syndrome when the accepted criteria are applied. At least one such case, brought to my attention by Paige,[19] was reported as Hodgkin's disease in an infant by Wollstein and McLean [20] in 1926. This case has been reviewed and in retrospect is thought to be a case of Letterer-Siwe's disease. In 1944 Jaffe and Lichtenstein [21] reported a case in an article on eosinophilic granuloma.

Early in 1940 Glanzmann [22] reported a case of Abt-Letterer-Siwe's disease in a 2-year-old female. Some features of this case, namely, osseous defects of the skull, exophthalmos, and presence of lipid in some of the granulomatous lesions, caused him to think that the condition was closely related to the xanthomatosis of Schüller-Christian's disease. Glanzmann regarded the case of Schultz, Wermbter, and Puhl [12] as a transitional form between Letterer-Siwe's and Schüller-Christian's diseases. Wallgren's [13] second case also presented some features of Schüller-Christian's disease (lipid deposit in macrophages and osseous defects of the skull). He postulated that there was an overlapping of the two diseases and that the rapidity of the course of the disease determined the amount of lipid deposited in the macrophages.

In an article on eosinophilic granuloma, Gross and Jacox [23] reported a case of Letterer-Siwe's disease which occurred in a 13-months-old child who died 5 months after onset of symptoms. At autopsy the lungs were thought to resemble those seen in Schüller-Christian's disease, but otherwise the clinico-anatomic complex was similar to that of Letterer-Siwe's disease. Gross and Jacox cited a case reported by Erber [24] in 1931 which they thought belonged in the category of reticulo-endothelial diseases. Siwe [3] did not include this case in his original series nor was it included by Abt and Denenholz [1] or by Wallgren [13] in their series. Lipid was described in some granulomatous lesions in this case and it was probably excluded by the above investigators for that reason.

A number of other cases displaying features of the two diseases and thus thought to represent transitional forms have been reported by Freund and Ripps [25] (1941), Galeotti Flori and Parenti [26] (1937), Freud, Grossman, and Dragutsky [27] (1941), and Sweitzer, Winer, and Cumming [28] (1939). Freund and Ripps reported a case as Schüller-Christian's disease which 14 months before death showed marked proliferation of reticulum cells and formation of syncytial reticulum giant cells in a lymph node taken for biopsy. A very small amount of lipid was present in the reticulum cells, but the diagnosis of Schüller-Christian's disease could not be made until the autopsy material was examined. Characteristic granulomatous lesions with numerous foam cells were found in the lungs and paravertebral fascia, but the lymph nodes

showed changes similar to those seen at biopsy. In their case a mass had appeared in the left groin at the age of 7 weeks but growth and development were normal until the age of 7 months, when pallor and anemia were noted. Later, areas of rarefaction in the skull were demonstrated by roentgenograms. The child died at the age of 2 years following perforation of a gangrenous appendix. The disease in this case was unusually protracted and supports Wallgren's [13] contention that the presence of lipid in the macrophages of granulomatous lesions is related to the duration of the disease. Freund and Ripps cited a similar case reported by Galeotti Flori and Parenti. Biopsy of a lymph node, 1 year before death of a 20-months-old child, showed marked reticuloendothelial hyperplasia, and the characteristic cells were devoid of lipid. At autopsy, typical lipid granulomas of Schüller-Christian's disease were found.

Freud, Grossman, and Dragutsky [27] reported a case of "acute idiopathic cholesterol granulomatosis," which in many respects was similar to Letterer-Siwe's disease. It occurred in a 7-months-old boy and was rapidly fatal (3 months). The observations at autopsy were similar to described cases of Letterer-Siwe's disease except that there was a large amount of lipid in the involved organs, namely, the thymus, lungs, liver, spleen, and lymph nodes. These investigators accepted their case as supporting Wallgren's [13] tenet that Letterer-Siwe's and Schüller-Christian's diseases are basically the same. The lipid content in this instance was greater than would be expected in a disease existing only 3 months.

Another example of a borderline case is given by Sweitzer, Winer, and Cumming.[28] A 3-year-old boy was well until the age of 2½ years when he complained of pain and weakness in the back and left leg, which limited his activities. Shortly thereafter cutaneous lesions of papular character appeared and anemia developed. Biopsy of the skin showed obliteration of the rete pegs with numerous nonlipid reticuloendothelial cells in the cutis. Biopsy of the left femur showed many large mononuclear cells, with abundant, finely granular, but only slightly vacuolated cytoplasm and multinucleated giant cells. At autopsy 45 days later many organs were involved with granulomatous lesions which resembled the nodules in the biopsy material.

Merritt and Paige [29] reported a case in which there was marked cutaneous involvement in a child, 3 years of age. Other symptoms had appeared approximately 1½ years earlier. At autopsy there was extensive hyperplasia of the reticulo-endothelial cells without evidence of lipid deposition in the lymph nodes and spleen, while cells of similar

lesions in the thymus, lungs, dura, and bones contained large amounts of lipid and were thought to be typical of Schüller-Christian's disease.

Another case of an intermediate type is that recorded by Grady and Stewart [30] in 1934. The disease occurred in a 3-year-old female who had been ill for approximately 2 years with "running ears." Of particular interest were the lesions in the spleen, some lymph nodes, and portions of the bone marrow, which resembled the granulomas of nonlipid reticulo-endotheliosis. Elsewhere, including the mastoid processes, the lesions were typical of Schüller-Christian's disease.

If the broader concept introduced by Glanzmann [22] and Wallgren [13] is accepted, at least one case (case 1), reported by Lane and Smith [31] in 1939 as "Schüller-Christian disease with cutaneous lesions," can be considered a transitional form bridging the gap between nonlipid (Letterer-Siwe's disease) and lipid reticulo-endotheliosis (Schüller-Christian's disease).

Jaffe and Lichtenstein [21] went further in an attempt to correlate nonlipid reticulo-endotheliosis (Letterer-Siwe's disease) with other diseases involving the reticulo-endothelial system, *i.e.*, idiopathic xanthomatosis (Schüller-Christian's disease) and eosinophilic granuloma. They believed that the different clinico-anatomic observations merely represent varying gradations of severity in the same process—Letterer-Siwe's disease showing the most severe and acute manifestations and being rapidly fatal, with little or no lipid deposition occurring in the reticulo-endothelial cells; Schüller-Christian's disease representing a chronic form of the same disease with a protracted course and the presence of typical foam cells in the lesions which have not been replaced by collagenous connective tissue; and eosinophilic granuloma being the most benign form of the disease with recovery usually occurring. Green and Farber,[2] and Farber [32] had previously suggested that the same basic disorder was responsible for the three diseases.

Several reported cases of reticulo-endotheliosis in adults, variously called aleukemic reticulosis, aleukemic monocytic leukosis, systemic reticulo-endotheliosis, are stated by the authors to resemble reticulo-endotheliosis in infants. Such a case was reported in an adult female, 36 years of age, by Ritchie and Meyer [33] in 1936. Goldzieher and Hornick [34] reported a case in a 75-year-old male and reviewed 22 similar cases appearing in the literature prior to 1931. Not all of these occurred in adults, as he included Akiba's [5] and Letterer's [4] cases. Dameshek's [35] case was in a 51-year-old man. Dameshek stressed the uniformity of the changes in the reticulo-endothelial system irrespective of age and cited cases that occurred from 11 days (Sherman [15]) to 75 years

of age (Goldzieher and Hornick [84]). As yet, there is no convincing evidence that the reticulo-endotheliosis occurring in adults is the same disorder as the infantile form under discussion.

Discussion

There has been considerable speculation and discussion concerning the etiology of Letterer-Siwe's disease. Siwe [3] divided into two categories the diseases of the reticulo-endothelial system not belonging to the then recognized xanthomatoses (Schüller-Christian's, Gaucher's, and Niemann-Pick's diseases). In the first group he included those cases associated with an acute infection known as infectious reticulo-endotheliosis; in the second group he placed those cases in which no significant infection was present, now known as Letterer-Siwe's disease. Both are regarded as nonlipid reticulo-endotheliosis. Because of the similarity of the histologic changes and the distribution of the characteristic lesions in infectious reticulo-endotheliosis and Letterer-Siwe's disease, Wallgren [18] justifiably challenged the belief that these are separate disease entities. He also presented arguments and evidence for believing that Schüller-Christian's disease is a chronic form of Letterer-Siwe's disease and that, as such, it should be removed from the xanthomatoses.

A critical analysis of the 3 cases reported in this paper indicates that Letterer-Siwe's disease is of noninfectious origin. In each instance, the cutaneous lesions, which I consider a most important and perhaps the earliest manifestation of the syndrome, were present at birth and antedated the fever. There is no reason to believe that an intra-uterine infection was present in any of the cases. Unfortunately, in none was the placenta examined, but there was nothing in the clinical course of the pregnancies to suggest prenatal infection. Case 1 had bilateral otitis media early in the course of the disease, but the possible involvement of the contiguous structures of the ear by reticulo-endothelial granulomas simulating an infectious process must be considered. Glatt,[36] Lichty,[37] and Grady and Stewart [30] described involvement of the middle ears and mastoid processes in Schüller-Christian's disease by granulomas which produced symptoms indistinguishable from chronic otitis media and mastoiditis. The disease was recognizable only after microscopic examination of material removed at operation or autopsy.

If fever is the criterion for infection, infection was present in all previously reported cases as well as in the three presented here, as temperatures above normal were recorded in all at some time during

the illness. In some the fever was of the Pel-Ebstein type often seen in Hodgkin's disease. An unexplained fever is also often present in leukoses. Since the etiology of these diseases is still unknown, no opinion can be expressed concerning the cause of the fever. Any disease, not primarily infectious, may be accompanied or complicated by concurrent or intercurrent infection, and this may occur also in Letterer-Siwe's disease.

Some anatomic features of these cases tend to support the hypothesis that Letterer-Siwe's and Schüller-Christian's diseases are variants of the same basic disorder. In case 1 there was roentgenographic evidence of skull defects similar to those described in Schüller-Christian's disease (Fig. 2). A number of cases have now been reported in which membranous bones of the skull were involved (Wallgren's [13] case 2, Glanzmann,[22] Abt and Denenholz,[1] and my case 1).

In all cases of the present series variable numbers of cells with vacuolated cytoplasm were found in the typical lesions in one or more sites, although in only one case (case 2) were they at all numerous. Microscopic examination of the spleen or para-aortic lymph nodes in case 2, without a study of additional sections from other organs, might have resulted in a diagnosis of Schüller-Christian's disease. This was also suggested by the appearance of the atypical cells obtained on splenic puncture. It is difficult to reconcile the presence of lipid-containing cells in these cases with Wallgren's hypothesis that the lipid deposit in the granulomatous lesions is a result of chronicity and occurs in the more slowly developing cases. This is especially true of case 3 which occurred in an infant who died at the age of 41 days. Obviously there are factors, other than duration of the disease, which determine lipid deposition. In all cases the thymus showed extensive fibroblastic proliferation and under conditions of chronicity may ultimately have undergone fibrosis and collagenization, features thought to be peculiar to Schüller-Christian's disease.

Another point of anatomic similarity between Letterer-Siwe's and Schüller-Christian's diseases is suggested by the occurrence of cutaneous lesions in approximately one-third of all cases of the latter (Rowland [38]) and in all reported cases of Letterer-Siwe's disease. All variations of the cutaneous eruptions, except the bronze pigmentation and lipid infiltration of the eyelids (xanthoma palpebrarum) described by Chester [39] and by Chester and Kugel [40] as occurring in Schüller-Christian's disease, have been noted in Letterer-Siwe's disease. Petechiae have been noted by all authors. Seborrheic eczema or seborrhea-like eczema was noted by Abt and Denenholz [1] and by Wallgren [13] (case 1).

Papular lesions were described by Wallgren in his case 2, and maculopapular lesions were observed in case 2 of the present series, as were also petechiae and bullous lesions, and a "polymorphous rash" in case 3.

Two or more conditions cannot be considered variants of the same pathologic process just because they are similar anatomically. They must also be similar clinically and have a common cause. All accepted cases of Letterer-Siwe's disease have occurred in infants and young children and have invariably been fatal. An estimated 30 per cent of the cases of Schüller-Christian's disease recover. Generally, Schüller-Christian's disease occurs in children and young adults, which may account for the different clinical outcome in about one-third of the cases. The rapidly fatal cases of Schüller-Christian's disease have occurred in children under 4 years of age. Some of these have shown inconstant amounts of lipid in the granulomatous lesions, and constitute borderline cases. The classical triad of Schüller-Christian's disease depends on the involvement of specific organs or structures by the granulomatous lesions and is encountered too infrequently to be of great value in establishing a diagnosis of that condition. It is not disconcerting that this triad has not been reported in Letterer-Siwe's disease. Glanzmann's [22] case, which had skull defects and unequal bilateral exophthalmos, might conceivably have developed diabetes insipidus if the course of the disease had been of longer duration.

No racial predominance has been noted in Letterer-Siwe's disease. When Rowland [38] reviewed a series of cases of Schüller-Christian's disease in 1928, he concluded that the disease occurred with greater frequency in members of the Jewish race. As increasing numbers of cases have been reported, this racial difference is no longer evident.[41]

The nature of the cells involved in both diseases has interested many investigators. That the principal cells are derived from the so-called reticulo-endothelial system is generally accepted. There is divergent opinion, however, concerning what causes these cells to proliferate. If the proliferation is neoplastic, more pleomorphism should be observed in the proliferating cells. These cells are remarkably uniform from case to case. The cells in the thymus showed the greatest variation. Gross and Jacox [23] reported pleomorphism of cells in the thymus and spleen of their case, suggestive of a sarcoma. The occurrence of mitotic figures in the three cases reported here probably represents rapid proliferation. If mitotic figures were more numerous and if they exhibited abnormal forms, neoplasia would be more tenable. As a rule the mitotic figures were infrequent in regions of reticulo-endothelial proliferation in the thymus, liver, and spleen. They were more common in the foci of re-

ticulo-endothelial cells associated with infection, *i.e.*, in lesions of the skin, tonsils, buccal ulcers, lymphoid tissue of small and large intestine. If, in the future, an infectious agent is implicated, the proliferation of reticulo-endothelial cells must be regarded as a hyperplastic response.

The relationship of eosinophilic granuloma to the two conditions considered above is not so clear although roentgenographically the osseous lesions in the three conditions are indistinguishable. Microscopically, the granulomas of eosinophilic granuloma bear a resemblance to the first two diseases. The most conspicuous constant feature is the presence of large atypical mononuclear cells, many exhibiting phagocytosis. Interspersed among these are variable numbers of eosinophils and giant cells. Foam cells may or may not be present and are usually in direct relation to the duration of the lesions. Clinically, the benign course and the regression and healing of the osseous lesions, either spontaneously or following curettage or radiation therapy, make it difficult to identify eosinophilic granuloma with Letterer-Siwe's and Schüller-Christian's diseases.

Otani and Erhlich [42] and Jaffe and Lichtenstein [21,43] reported lesions of eosinophilic granuloma occurring in long bones and skull. They emphasized the seemingly benign course of the disease. Green and Farber [2] suggested that visceral lesions probably do occur because eosinophils were found in a lymph node biopsy from one of their cases and they advised that a guarded prognosis should be given. Dundon, Williams, and Laipply [44] were of the same opinion. Curtis and Cawley [45] have reported a case of eosinophilic granuloma of bone with cutaneous manifestations of the disease verified by biopsy. Weinstein, Francis, and Sprofkin [46] recently have reported a case with multiple osseous lesions of eosinophilic granulomatous type. The case had roentgenographic evidence of pulmonary infiltration similar to that seen in Schüller-Christian's disease. The patient recovered from the osseous and pulmonary lesions.

Jaffe and Lichtenstein [21] stated that eosinophils are found only in the osseous lesions of Letterer-Siwe's disease. In all three of my cases, eosinophils were found in visceral as well as skeletal granulomas. Eosinophils also occur in the granulomatous lesions of Schüller-Christian's disease. Gross and Jacox,[23] in a review of 84 cases of Schüller-Christian's disease, found that eosinophils occurred in variable numbers in 29 cases. Fraser's [47] article on skeletal xanthomatosis contains several colored drawings of typical granulomas of Schüller-Christian's disease, which are indistinguishable from the lesions of eosinophilic granuloma. Thannhauser [48,49] contended that eosinophilic granuloma of the bone is

the "monosymptomatic form of a well known systemic granulomatous disorder [Schüller-Christian's disease] in which histiocytes, eosinophils and xanthoma cells are observed in the lesion at different phases." Jaffe and Lichtenstein [50] believed that it is necessary to make a clinical distinction between eosinophilic granuloma of bone and Schüller-Christian's and Letterer-Siwe's diseases even though morphologically they apparently represent different phases of the same basic disorder.

Conclusions

Including the 3 cases reported in this paper, the number of cases which meet the established criteria for Letterer-Siwe's disease does not exceed 24.

This study has not disclosed the cause of Letterer-Siwe's disease, but it does offer evidence that the disease is not initiated by infection. In all cases, the cutaneous lesions preceded by 2 to several weeks the manifestations of infection, *i.e.*, sore throat, otitis media, diarrhea, and fever. Infection must therefore be considered secondary or intercurrent, and not causative.

That Letterer-Siwe's and Schüller-Christian's diseases represent different manifestations of the same basic disorder of the reticulo-endothelial system seems probable from the number of borderline or transitional cases which have been reported. Twelve such cases were found in a review of the literature. That such a relationship does exist between these two diseases is accepted by Green and Farber,[2] Jaffe and Lichtenstein,[50] Mallory,[51] and Letterer,[52] as well as by Wallgren.[13]

That a possible relationship exists between the above two conditions and eosinophilic granuloma has been suggested by the same investigators. Thannhauser [48,49] believed that eosinophilic granuloma is actually a phase of the disorder known as Schüller-Christian's disease and as such should not be considered as a separate clinical entity.

Regardless of the morphologic similarity among the three diseases, the clinical course of eosinophilic granuloma varies so greatly from that of the other two conditions that a sharp clinical distinction between these disorders of the reticulo-endothelial system is justified until a common etiologic factor has been demonstrated for all.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 7

FIG. 1. Case 1. Lateral view of body showing numerous cutaneous lesions confined chiefly to the torso. Many have hemorrhagic centers.

FIG. 2. Case 1. Roentgenogram of skull showing osseous defects in the right parietal and occipital bones.

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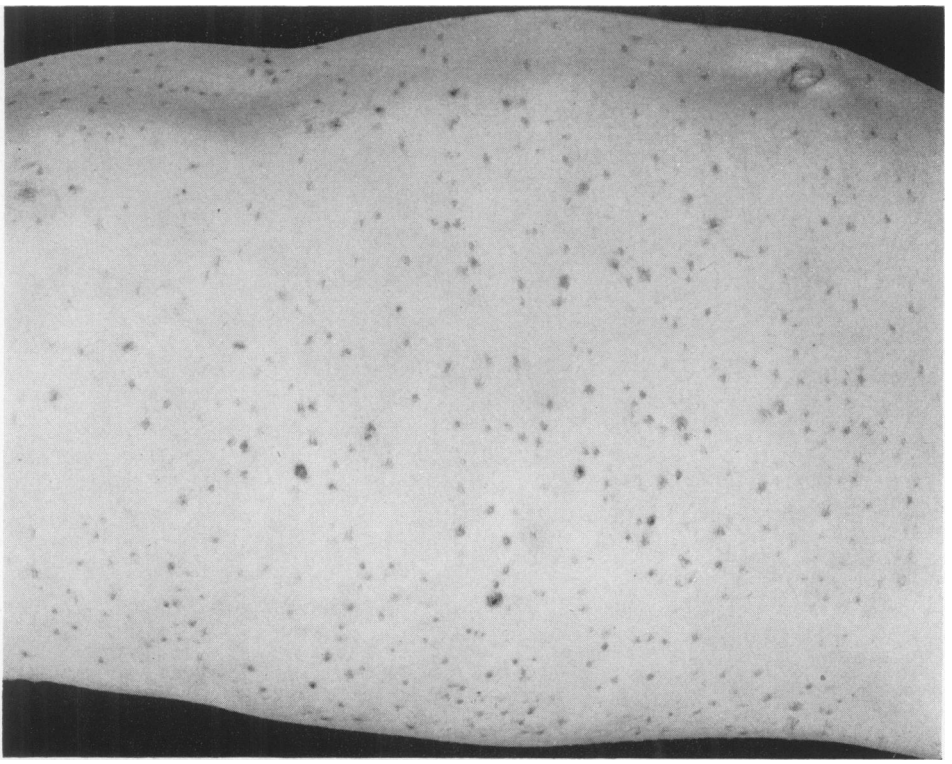

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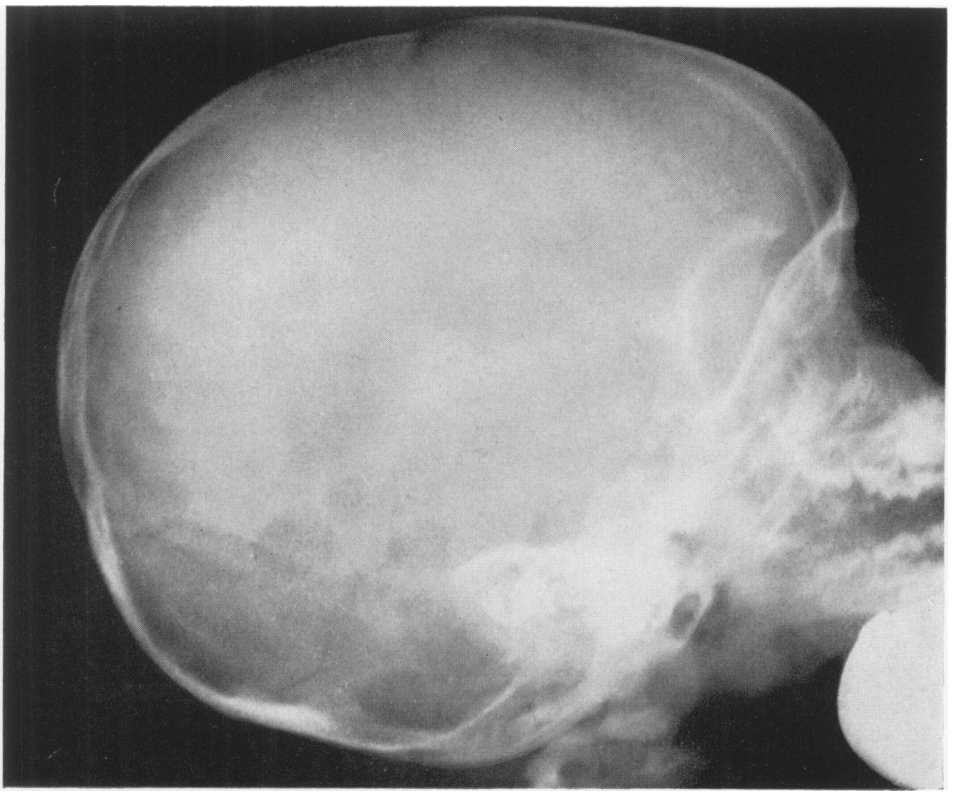
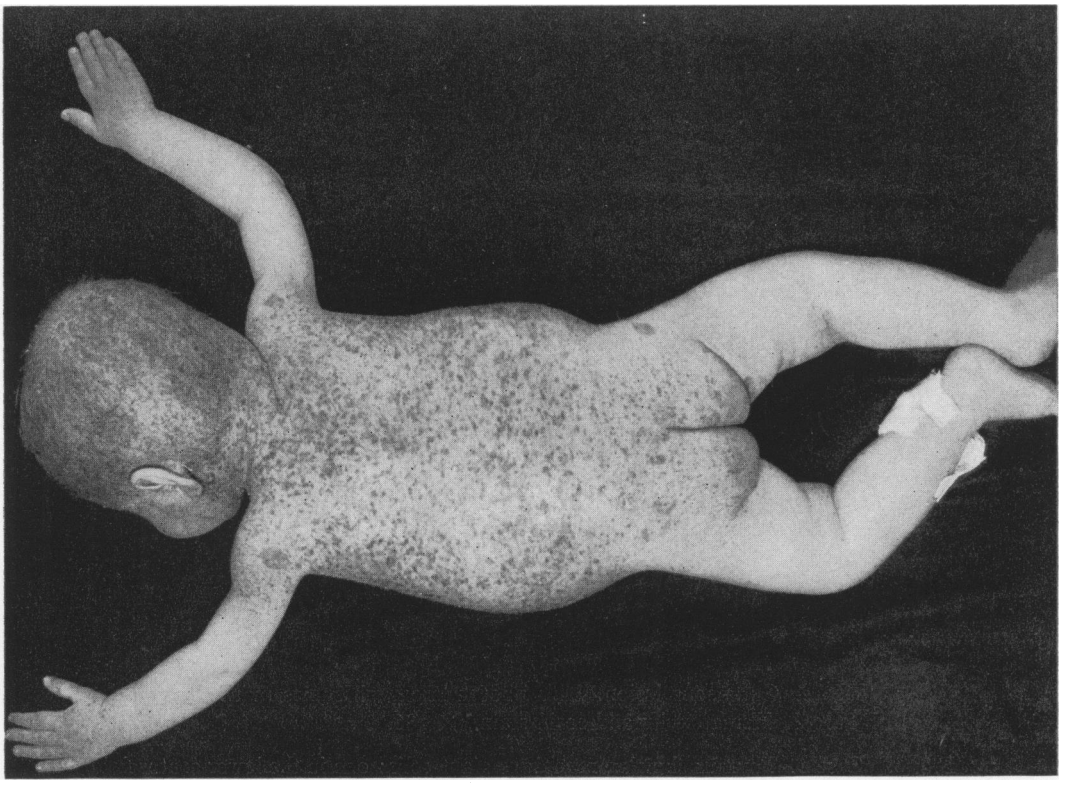


PLATE 8

FIG. 3. Case 2. Dorsal view of body to show diffuse involvement of trunk and scalp with cutaneous lesions. The extremities were spared in this case. The lesions were crusted maculopapules and petechiae. The increased transverse diameter of the body below the level of the ribs is due to hepatic and splenic enlargement.

FIG. 4. Case 1. Cutaneous lesion, showing a collection of atypical mononuclear cells in the corium and atrophy and parakeratosis of the overlying epithelium. There is a minute abscess in the epithelium. For comparison with the photomicrograph of the cutaneous lesion in case 2 (Fig. 5). Hematoxylin and eosin stain. × 186.

3



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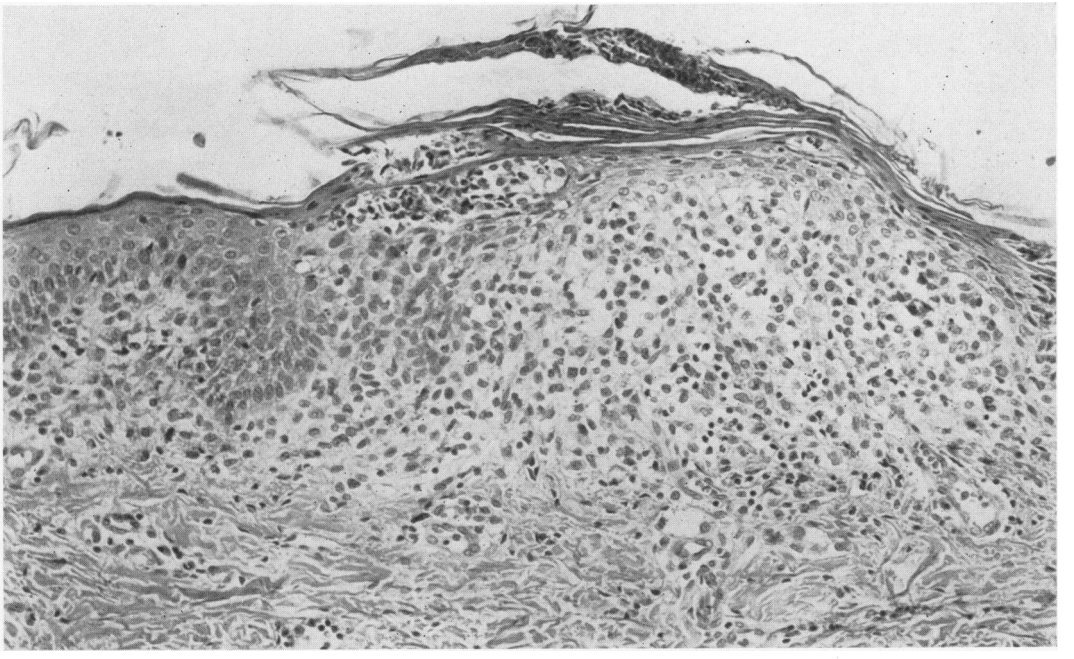
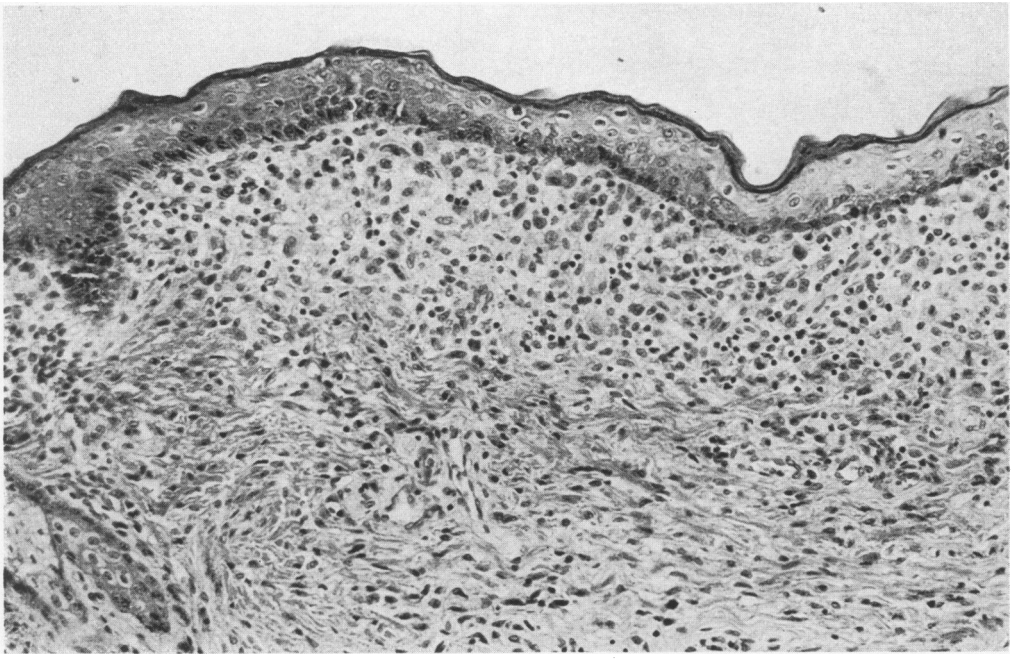


PLATE 9

FIG. 5. Case 2. Cutaneous lesion. This photomicrograph shows marked similarity to Figure 4. Hematoxylin and eosin stain. × 186.

FIG. 6. Case 1. Thymus showing numerous giant cells; one in the lower center field shows marked phagocytic activity. Of note are the characteristic mononuclear cells with vesicular nuclei and the irregular outline of the giant cells and mononuclear reticulo-endothelial cells. Hematoxylin and eosin stain. × 342.



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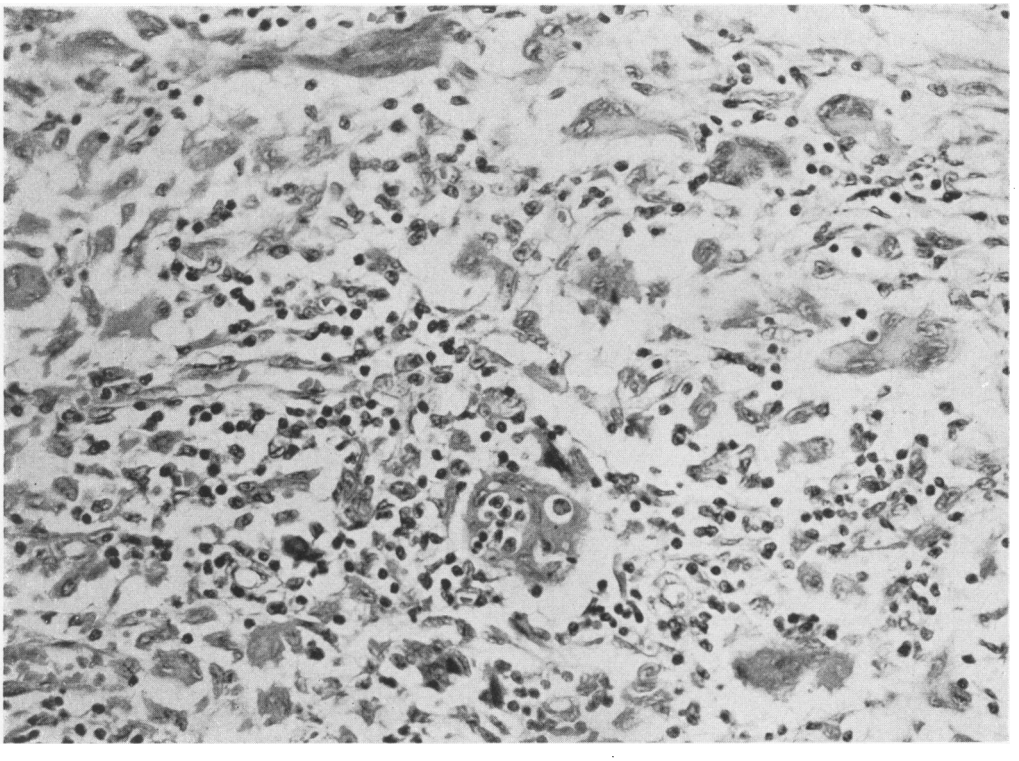

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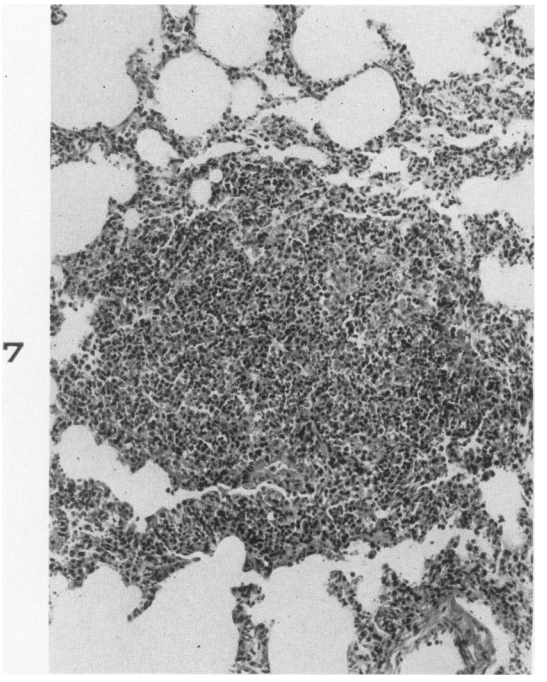
Plate 10

Fig. 7. Case 3. Lung showing a characteristic nodule of reticulo-endothelial cells. Similar cells are present in alveolar septa. Hematoxylin and eosin stain. × 80.

Fig. 8. Case 1. The subepithelial infiltrate in the base of the gingival ulcer. Several mitotic figures are present at A; fibroblastic proliferation and bizarre-shaped nuclear form at B. Hematoxylin and eosin stain. × 342.

Fig. 9. Case 1. Peyer's patch of the ileum completely replaced by large mononuclear cells. The small, dark cells are lymphocytes. Hematoxylin and eosin stain. × 186.



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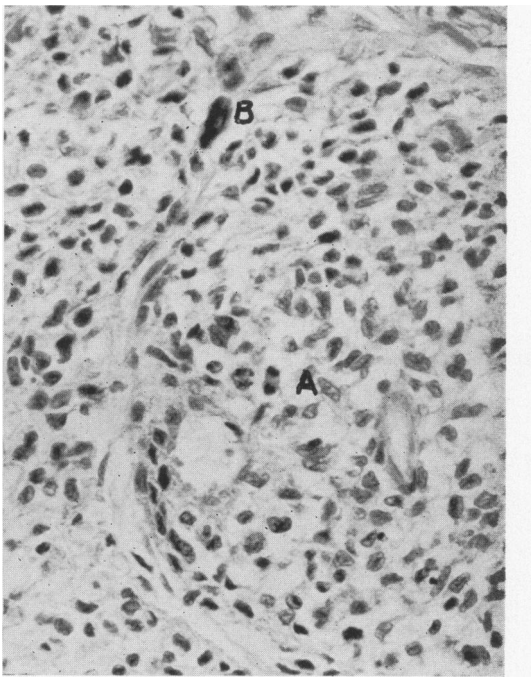

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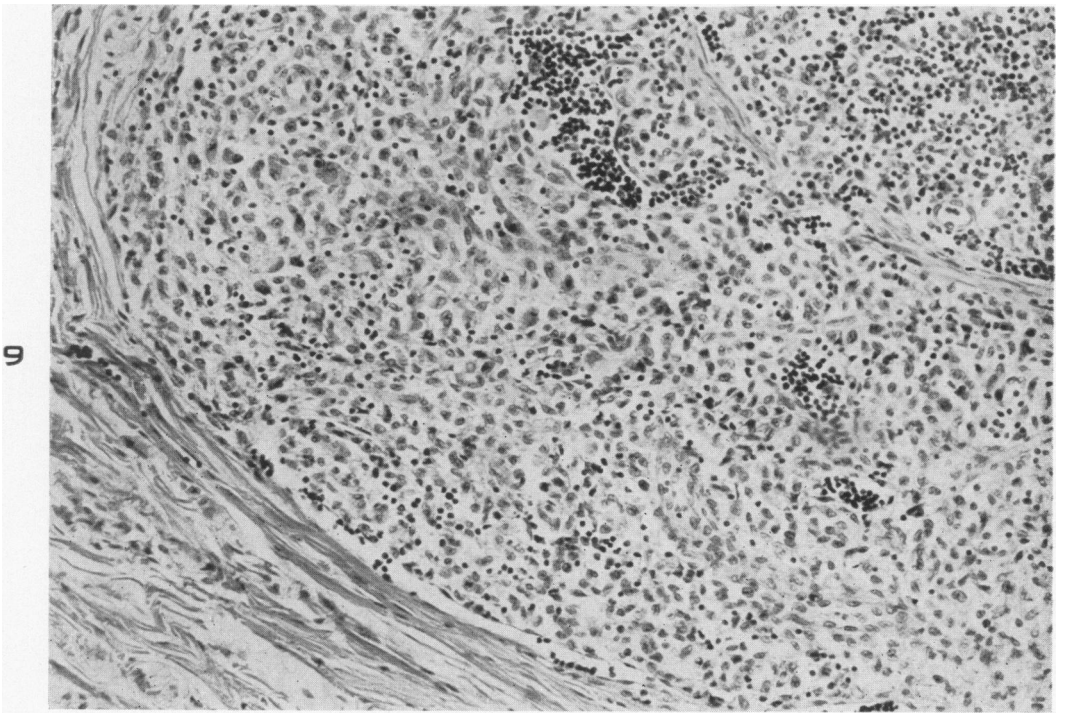

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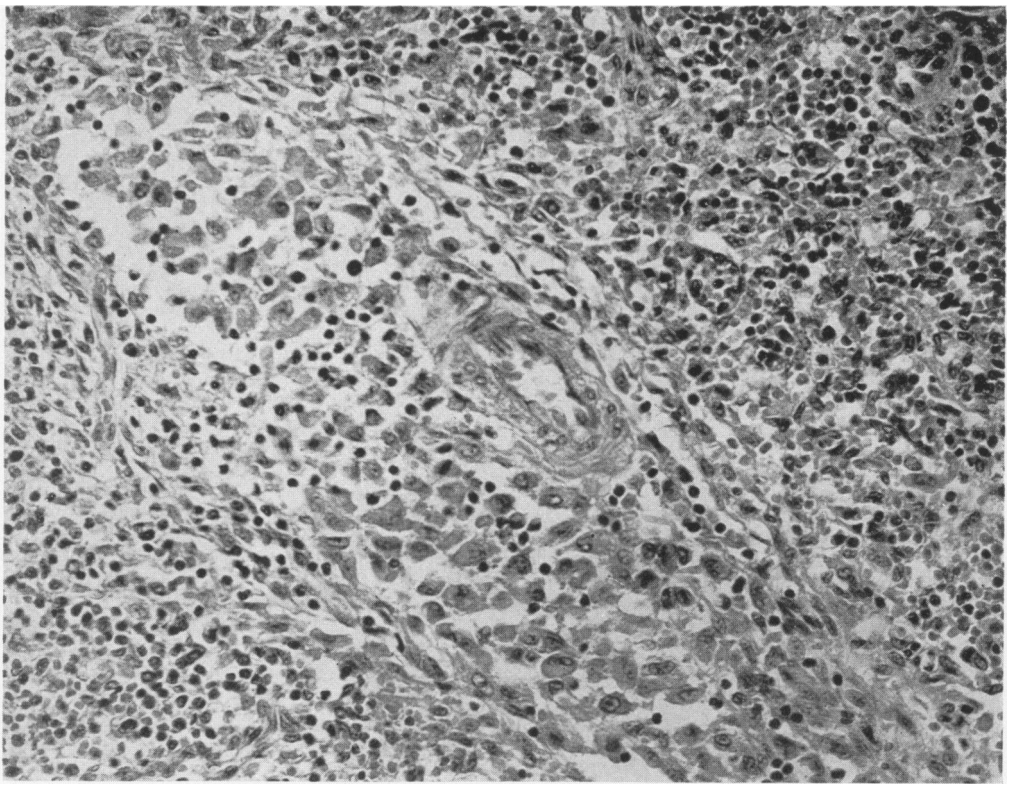
PLATE 11

FIG. 10. Case 1. A nodule of mononuclear cells near a central arteriole in the spleen. There is fibroblastic proliferation surrounding the nodule. A variety of cells may be seen in the splenic pulp. Hematoxylin and eosin stain. × 342.

FIG. 11. Case 2. Lymph node showing collections of large mononuclear cells, some of which have vacuolated cytoplasm, others contain phagocytized cells. Hematoxylin and eosin stain. × 342.

10



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